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RESURRECTION OF WHIOLE PANCREATICODUODENAL TRANSPLANTATION AT THE UNIVERSITY OF PITTSBURGH

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Thank you for including me in this illustrious group of speakers. Perhaps I should make clear that the title of my talk was furnished by the organizing committee. I can only assume that my good friend, John Najarian, came up with the resurrection idea. Normally, resurrections require the presence of saviors who end up being crucified. Once the facts surrounding our 1984 article (1) are revealed, I hope to be stripped of my savior status, or at least the martyrdom.

The Seminal Lillehei Papers

Where our 1984 contribution came from is best understood by starting with the landmark paper presented by Rich Lillehei to the American Surgical Association (ASA) on April 27, 1970 (2). Lillehei briefly mentioned his earlier unsuccessful case of segmental pancreas transplantation (with Bill Kelly) (3), before getting to his 10 whole organ procedures. Venous drainage from the pancreatiocoduodenal grafts was directed into the iliocaval system. In the first 4 whole organ recipients, exocrine secretions from the pancreas were exteriorized with a skin duodenostomy (2).

In cases 5 through 10, the proximal end of the graft duodenum was closed, and the distal duodenum (or adjacent jejunum) was anastomosed as part of a composite Roux limb to the host jejunum. In 9 of the 10 cases, a kidney also was transplanted. By the time of the ASA meeting, 8 of the 10 recipients had died. A ninth, who was only 90 days postoperative, succumbed shortly thereafter. The only bright note was the first-ever one year survival of an insulin-free pancreas recipient. However, this patient also died just after passing the one year milestone.

I was at that ASA meeting. In part because I was the next speaker on the program, I was concerned with what I perceived to be a sullen, if not frankly hostile, audience. When Lillehei finished, there was almost no applause, and

only 2 discussions (both of which were recorded and published [2]). The inference from the first discussion by John Brooks from the Brigham was that the Boston group did not believe that pancreas transplantation, upon which they also were working, was well enough developed to warrant a clinical trial. The other discussant was John Connolly from Irvine, California. He commended Dr. Lillehei for *"his ingenuity and possible (sic) foresight in initiating pancreatic transplantation"*. Connolly also recommended, *". . . trimming the donor duodenum down to a tuft for anastomosis to recipient bowel."*

I knew Rich Lillehei well enough to realize how shaken he was by this and his subsequent experience with the procedure. He performed 3 more whole organ pancreas transplants during the next 3 years, none with companion kidneys (4). In the last case, the donor duodenum was discarded except for a patch surrounding the ampulla of Vater as had been suggested by Connolly at the ASA meeting (discussion of [2]). When these last 3 grafts were rejected or were lost to vascular thrombosis, an end had come to what David Sutherland has called *"Epoch Zero (i.e. The Prehistorical Epoch)"* of the Minnesota experience. A 5 year moratorium was self-imposed by the Minneapolis team.

Segmental Pancreas Transplant Pioneers

During the 5 years of the Minnesota moratorium, the concept of whole organ transplantation was abandoned, or even villainized, worldwide. However, the use of segmental grafts kept the embers of pancreas transplantation alive: Gliedman in New York (5), Lagardier in Zurich (6), Groth in Sweden (7), and Dubernard in Lyon (8). With the assumption that enteric exocrine drainage was the principal lethal risk, various strategies were developed to divert the exocrine secretions of the segmental grafts into extra-alimentary channels (for example, host ureter or peritoneal cavity) or to block the secretions with polymer injections. Abandonment of enteric drainage was resisted mainly in Stockholm by Groth

(7,9) but also by Largardier in Zurich (6). The techniques used in Stockholm all involved drainage into host jejunal Roux limbs (10).

The Resurrection

The 8 years of David Sutherland's "historical Epoch 1" began with resumption of the Minnesota program and were bracketed by 1978 and 1986. After the seminal trial by Calne in Cambridge (11), cyclosporine became available in selected centers in 1980. After testing the new drug in Pittsburgh in Lillehei's canine pancreas transplant models, we concluded our 1984 experimental report (12) with the following sentence: *"We suggest that pancreaticoduodenal transplantation, which was abandoned 10 years ago, be reconsidered for clinical application."*

In fact, the first 2 human recipients in our clinical report of 1984 (1) had been treated in early 1983. We drained the exocrine secretions through the graft duodenal C-loop and a short segment of jejunum into the host jejunum. Except for the graft jejunum, the Roux limb was the same as in Lillehei's procedure (Figure 1A,B). The spleen was included with the pancreas in one of these cases (Figure 1A), but later removed because of hypersplenism. Both patients developed episodic fevers, cramps, watery diarrhea, a protein-losing enteropathy, hypoalbuminemia, and anemia (1). Some of these complaints resembled the blind loop syndrome that I had studied 25 years earlier, including in patients with stagnant Roux limbs following gastric surgery (13).

Because of these similarities, and because we also were exploring the possibility of intestinal transplantation, the grossly normal Roux limb of the graft was detached for physiologic studies and anastomosed to the skin (Figure 1C). Over the next 42 days, the daily ostomy output was 2 to 3 liters, containing up to 20 grams per liter albumin (1). The total loss of 40 to 60 grams per day of endogenous albumin exceeded that of a lethal nephrotic syndrome in a patient

with kidney disease. Endoscopic biopsies of the allograft duodenum revealed mucosal damage, acute and chronic inflammation, and ulcerations, with minimal or no involvement of the muscularis or serosa.

In addition to its metabolic consequences, the duodenum was an obvious entry site for microorganisms. All of the graft bowel was removed except for a duodenal bubble that was anastomosed to the host jejunum (Figure 1D). The same revision was then done in the second patient. Both recipients were promptly relieved of their problems. All further patients had duodenal bubbles from the outset (1,14).

Dissemination of the Whole Pancreas Procedure

I presented our whole pancreas transplant cases in a peripheral session at the First International Symposium on Cyclosporine, hosted by Barry Kahan in Houston in May 1983. In his scholarly historical account, Sutherland described the prompt action taken by the Minnesota team: *"By mid-1983, we stopped doing cadaver segmental grafts as a routine and returned to the whole pancreas technique (with papilla of Vater) used by Lillehei in his last case. We performed only a few cases by this technique before following the lead of Starzl et al at Pittsburgh to include the entire duodenum, as originally described by Lillehei."* (15). The last 7 words were slightly confusing since the duodenal bubble, rather than the entire duodenum, was what was meant.

Because pancreas transplantation, whether segmental or whole, had been opposed by our Pittsburgh Department of Medicine, the number of cases done in Pittsburgh was small. Thus, the reinstitution of whole organ transplantation in Minnesota was a critical step in disseminating the use of the operation. Spread of the procedure also was strongly influenced by 2 men who had scrubbed on our 1983-84 operations. One was a transplant fellow, Munci Kalayoglu, who subsequently joined Hans Sollinger at the University of Wisconsin. In Madison,

Sollinger had compiled a discouraging series of segmental pancreas transplantations in which exocrine secretions were drained by duct anastomosis to the bladder (16). After Kalayoglu's arrival in Madison, whole organ transplantation was adopted (17). However, exocrine secretions were drained into the urinary tract by connecting a patch of duodenum surrounding the ampulla of Vater to the bladder.

The second export of the Pittsburgh experience was via Robb Corry who had been on a sabbatical leave in Pittsburgh to gear up for a new liver transplant program at the University of Iowa. As a bonus, Corry participated in several pancreaticoduodenal transplantations and applied this whole organ operation immediately after he returned home to Iowa City. For the first year and a half, Corry drained the duodenal bubble into the jejunum, just as he had seen in Pittsburgh (18). But in subsequent cases, the Iowa group anastomosed the duodenal bubble to the bladder (19). As recalled by Nghiem (20), the switch to bladder drainage in Iowa was undertaken independently by him while Corry was on temporary leave in West Virginia.

Interactions between the Iowa City, Madison, and Minneapolis groups ensued that can be best appreciated by perusal of Groth's textbook, Pancreatic Transplantation (1988), to which all 3 teams contributed. In the Wisconsin chapter, Sollinger was still using a patch of duodenum for bladder anastomosis (21), but shortly afterwards, converted to use of the duodenal bubble (22). In his 1993 report to the American Surgical Association, Sollinger noted that this bladder technique had spread like wildfire and was being employed in 71 United States pancreas transplant centers (23). Minnesota was no exception. In the Minnesota chapter of Groth's 1988 book, Sutherland et al stated that, *"We have not used enteric drainage for a cadaver pancreas graft since June 1986 and have nearly completely converted to the use of a bladder technique for transplant from cadaver donors."* (24).

Despite the unwavering advocacy of enteric drainage by Groth (7 9, 10, and discussion of ref [23]), bladder drainage retained dominance for more than a decade. Because of a myriad of problems necessitating conversion to enteric drainage (scrupulously reported by Sollinger [23]), enthusiasm for bladder drainage began to diminish by the early 1990s. By then, Corry (now on the University of Pittsburgh faculty) switched back to enteric drainage of the duodenal bubble (25) and became the first proponent of tacrolimus for pancreas transplantation (26,27). Coinciding with the widespread acceptance of tacrolimus, enteric drainage became the reconstruction of choice at the pioneer centers and most others (15,28).

Pancreaticoduodenal Transplantation: A Finished Product?

Can we conclude that the pancreaticoduodenal operation has finally been standardized? Not really. It is well known that first pass exposure of the liver to insulin is critical for normal glucose homeostasis. Insulin also is essential for maintenance of liver size, ultrastructure, function, and the capacity for regeneration (29-32). To confer these so-called "hepatotrophic" benefits of insulin upon a co-transplanted liver, a cardinal principle in liver transplantation, and in the various multiple abdominal organ transplant procedures shown in Figure 2, is to drain the venous blood from the native pancreas or from a co-transplanted pancreas into the portal or mesenteric vein.

Because a significant number of liver recipients have preexisting Type I diabetes, it is surprising that less than a dozen cases have been reported of pancreas transplantation in diabetic liver recipients (33). In the first case, a polymer-injected segmental graft was transplanted in the pelvic location by Roy Calne on October 3, 1979, with systemic venous drainage (11). The pancreas failed at one year, but the patient lived for another 5 years before dying of liver

failure. Nine years passed before the second combined liver-pancreas procedure was performed on July 1, 1988 in Pittsburgh (34).

The Pittsburgh patient was a 40 year old male with end stage chronic HBV hepatitis who had been on 70 units/day insulin for many years. After hepatic replacement with conventional techniques (Figure 3, above transverse line), the donor's pancreas was arterialized below the transverse mesocolon with a Carrel patch (Figure 3, bottom). For the first time to our knowledge, the venous blood from a whole pancreas graft was drained into the portal bed (in this case via the host superior mesenteric vein) (Figure 3). Despite recurrent hepatitis, the patient is well and is insulin-free after 18-1/2 years (34). A second noteworthy feature of this operation was that all of the graft duodenum and a short piece of donor jejunum were retained and used as a Roux limb that was emptied with the proximal and distal enteric anastomoses as shown in Figure 3.

The Roux limb was no longer an Achilles heel for the simple reason that it was protected from immune injury by the better immunosuppression that had become available with cyclosporine. This conclusion, which was tentatively reached with the case shown in Figure 3, was verified later in 1988 and 1989 in a series of cancer patients who had removal of all upper abdominal organs, followed by en bloc liver and pancreas replacement (35). In some of these cases, the duodenal loop and downstream jejunum were used as a Roux limb, as in Figure 3. But in others, the allograft bowel became part of the mainstream gastrointestinal track (Figure 4). These were the first-ever examples of truly long survival of a functional bowel allograft in a human recipient. Despite a high rate of tumor recurrence (33), several of these patients are still alive and insulin free more than 18 years later.

The observations made with the operations shown in Figures 3 and 4 demonstrated the remarkable versatility of the pancreaticoduodenal graft, with or without a jejunal extension. The use of the whole pancreas in continuity with a

liver allograft (Figure 4) is rarely used today for cancer treatment. However, this en bloc procedure has had its own recent resurrection for the treatment of Type I diabetics who also need liver replacement for non-neoplastic hepatic disease. The operation was used recently for this purpose by Pirenne et al (33) in Brussels and by Young et al (36) in Leeds. The only difference from the cancer operation is that the pancreaticoduodenal graft is layered on top of the native pancreas and duodenum which are not removed. In these operations (Figures 3 and 4) and in the more complex multiple organ procedures shown in Figure 2, the pancreatic venous drainage goes straight to the liver. The exocrine secretions are emptied into the host duodenum or jejunum by the Roux limb originally described by Lillehei.

The Physiologic Liability Of Abnormal Anatomy

Widespread acceptance that non-physiologic exocrine drainage of pancreas grafts was not a desirable option required nearly a quarter century. A similar but more subtle question about pancreas transplantation concerns the optimal route of the allograft's venous drainage. Concerns of the liver surgeon about pancreatic venous drainage have, of course, been largely focused on the welfare of the co-transplanted liver (29-32). Any such discussion may also be relevant to the long term health of diabetic recipients of pancreas-only or pancreas-kidney transplantation. After a portacaval shunt in non-transplant patients, there are major pathologic changes in the liver (37), similar to these caused by this procedure in dogs, baboons, and other animals (38) (Figure 5). With electron microscopic (EM) studies obtained only a few days after portacaval shunt, only a few fragments of rough endoplasmic reticulum can be found in the shrunken hepatocytes. These and other ultrastructural changes correlate with wide-ranging losses of liver function. The association of these abnormalities with diversion of endogenous insulin around the liver has been demonstrated with simple experiments in dogs and other species (29-32, 38,39).

The liver cannot survive for long without insulin. With systemic venous drainage of the pancreas, this need is met (albeit sub-optimally) by the immediate development of arterial hyperinsulinemia, the maintenance of which theoretically could exhaust a transplanted pancreas. The metabolic penalties of placing the pancreas in a non-anatomic location go far beyond the simple loss of normal glucose homeostasis. Not surprisingly, systemic drainage of the transplanted pancreas has been associated by some members of this audience with dyslipidemia, accelerated atherosclerosis, and insulin resistance (40). In turn, insulin resistance is thought to be a seminal factor in nonalcoholic steatohepatitis syndromes (NASH liver disease) (41), the first stages of which have hepatic lipid accumulation similar to that shown in Figure 5 (mid panel). Formal assessment of such metabolic derangements would require very long follow-ups --- perhaps decades. Studies of this kind in systemically-drained pancreas recipients have not been done.

The Foundation Laid by Lillehei

It is only appropriate to conclude these historical remarks by returning to Rich Lillehei. His death in 1981 was particularly tragic because he never saw the fruits of his grand vision, and especially the ultimate vindication of his whole pancreas operation. In his ASA report of 1970 (2), Lillehei ascribed about half of the deaths to idiosyncratic events: for example contaminated ALG, a stroke, electrolyte imbalance, etc. However, he ultimately came to believe that the problems were more those of bowel transplantation than of the pancreas per se. This was evidenced by his elimination of everything but the duodenal patch in his last case.

Lillehei's insight is easier to understand if we bear in mind that he also was the modern forerunner of intestinal transplantation. Nearly 50 years ago, and 11 years before his epochal 1970 pancreas paper, Lillehei brought his

studies of canine intestinal transplantation to the altar of the American Surgical Association, with an equally cool reception (42). Forewarned, Owen Wangensteen (Lillehei's chairman) pre-empted opposition with a memorable quotation. *There may be those who might suggest that this work represents only a stunt. I will remind you that Benjamin Franklin once asked in passing judgment upon the promise of a matter of debatable merit: "What is the good of a newborn baby?" Well, who can tell?*

Lillehei's misfortune was that by arriving a decade too early, he encountered the insurmountable obstacle to intestinal and pancreas transplantation: i.e. inadequate immunosuppression. It was bad enough to die so young, but the worst heartbreak was to die disappointed. I skied with Lillehei from time to time in Colorado during the 1960s and 1970s. Once, in a darker moment, he ruefully remarked that he might have really accomplished something if only he had concentrated on fields less frustrating than pancreas and intestinal transplantation. Of course, this historical meeting is a living testament to how much he actually did accomplish.

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FIGURE LEGENDS

Figure 1 --- Pancreaticoduodenal transplantation performed in 2 patients (top left and right) in early 1983. The spleen was included in the first case, but removed 6-1/2 days later. The graft jejunal limb was detached and brought to the skin in patient 1 (bottom left), and in both cases was subsequently converted to a duodenal bubble (bottom right). The duodenal bubble was constructed at the outset all subsequent cases.

Figure 2 --- Different multiple abdominal visceral (multivisceral) procedures in which a transplanted or native pancreas has venous drainage into the splanchnic venous bed.

Figure 3 --- The liver-pancreas transplant operation performed on 1 July 1988. Key features included the interposition of the transverse mesocolon between the 2 separately revascularized organs, delivery of the pancreas graft venous outflow into the host superior mesenteric vein (SMV), and the method of enteric drainage of pancreatic exocrine secretions. With slight modifications (e.g. double exocrine drainage is not necessary), the pancreas engraftment technique could be used to test the value of portal pancreatic venous drainage in pancreas-alone or pancreas-kidney recipients. PV: portal vein. IVC: interior vena cava. (By permission of Harary et al: Liver Transplantation, 2007)

Figure 4 --- (Left) Gastrointestinal series obtained in a patient treated with upper abdominal exenteration in 1988. Note that the homograft duodenum and a short segment of jejunum are in continuity with the patient's own stomach and jejunum. (Right) Technique used. To preserve the recipient celiac axis and left gastric artery, it was necessary to place the donor Carrel patch below the left renal vein and the recipient superior mesenteric artery.

Figure 5 --- Photomicrographs of sections from a baboon liver subjected to portal diversion. The panels on the left show the liver structure as seen in a biopsy immediately before portacaval anastomosis. The panels on the right show the condensation of lobular reticulin, accumulation of fat and atrophy of hepatocytes 208 days after operation. (Top) reticulin stain, X20; (middle), frozen section stained with Sudan, 4, x30; (Bottom), and E, x175.

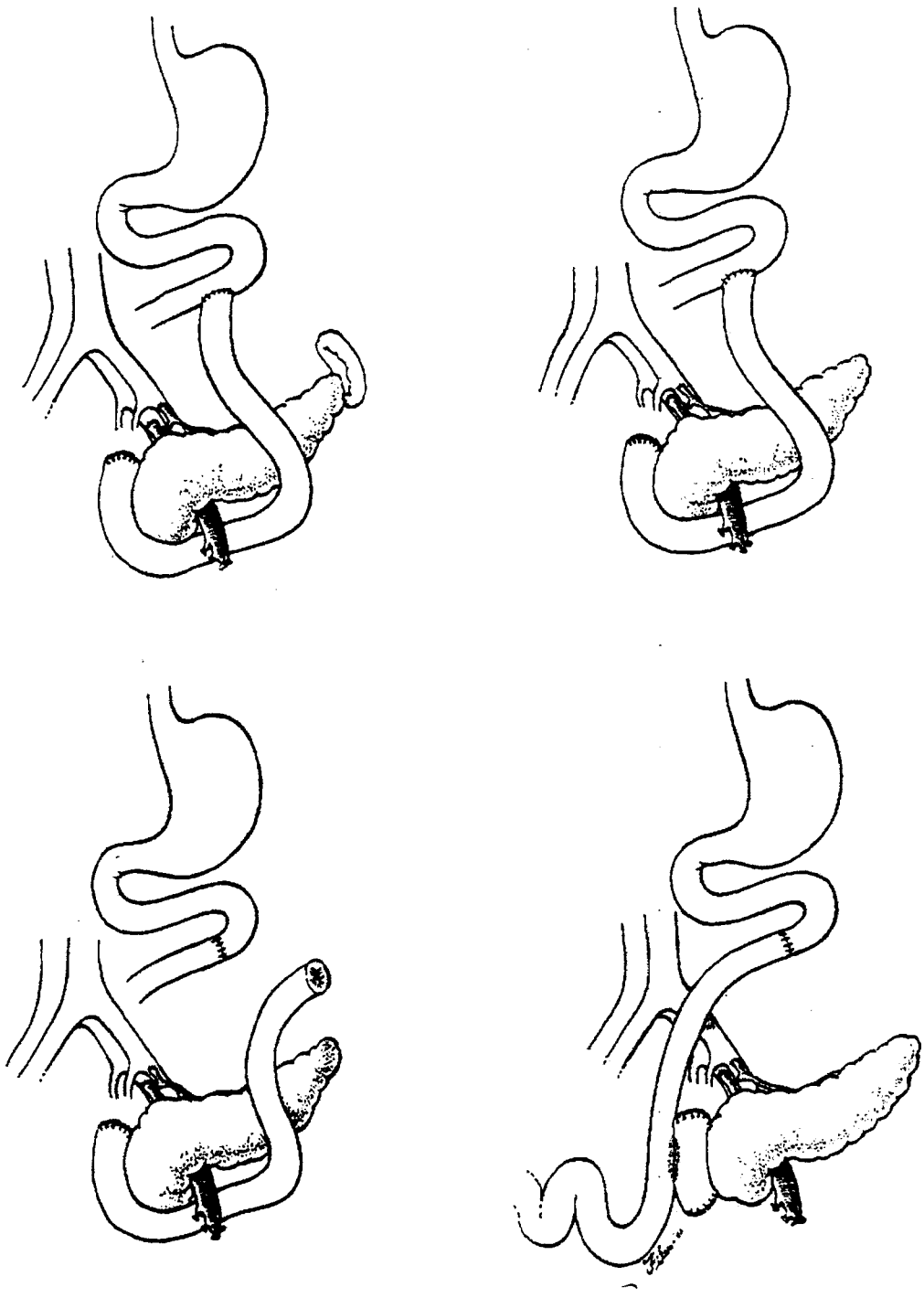


Figure 1

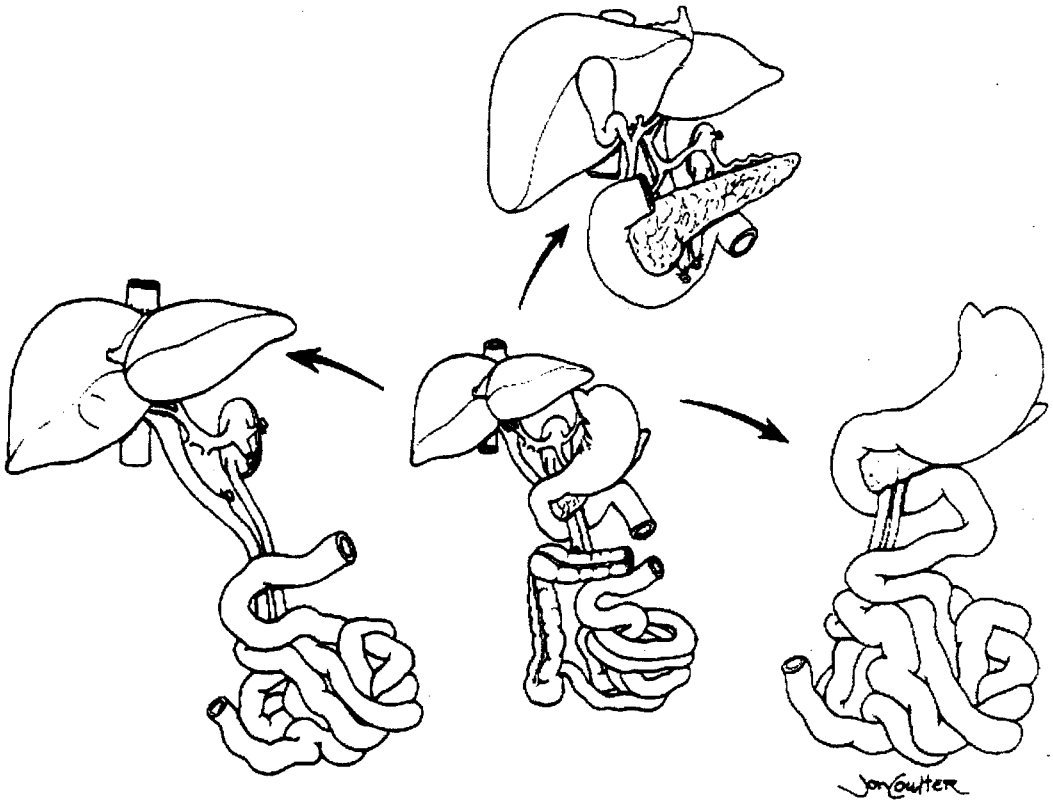
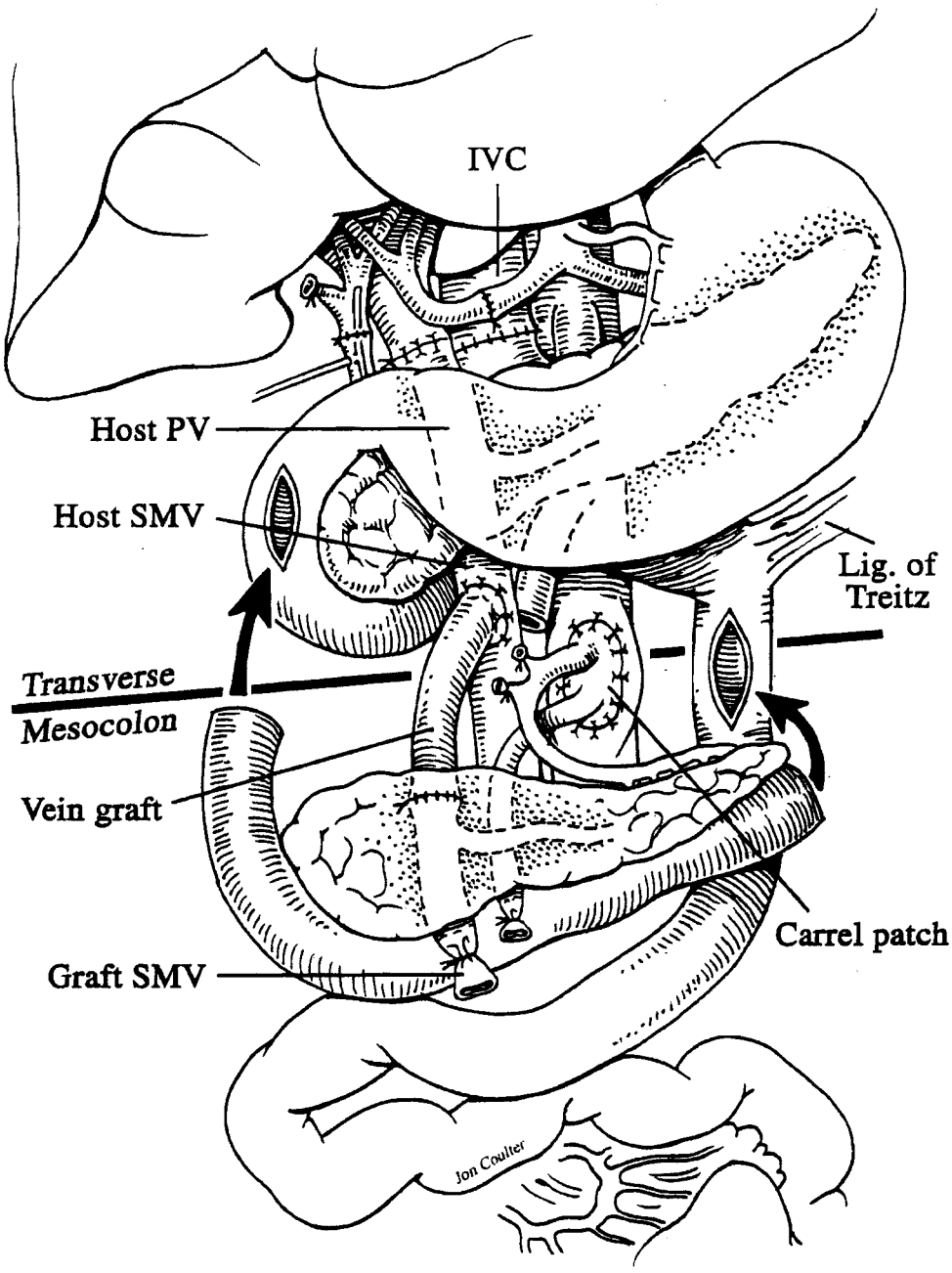


Figure 2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Jon Coulter

Figure 3

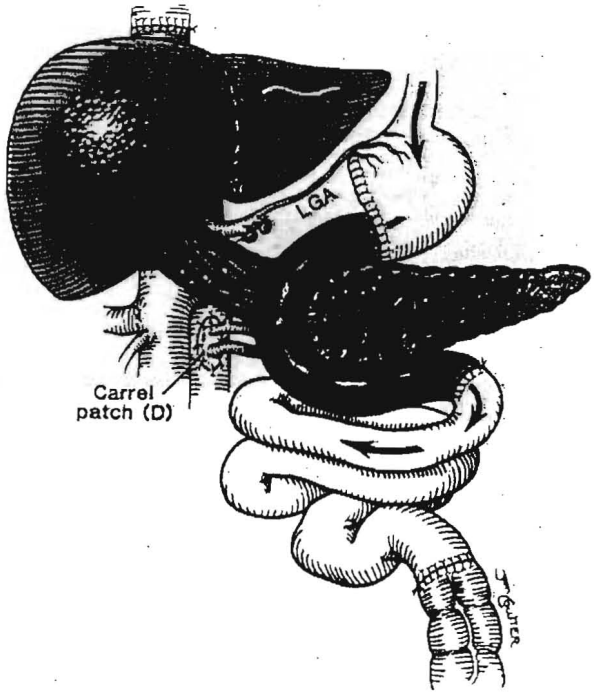

Figure 4